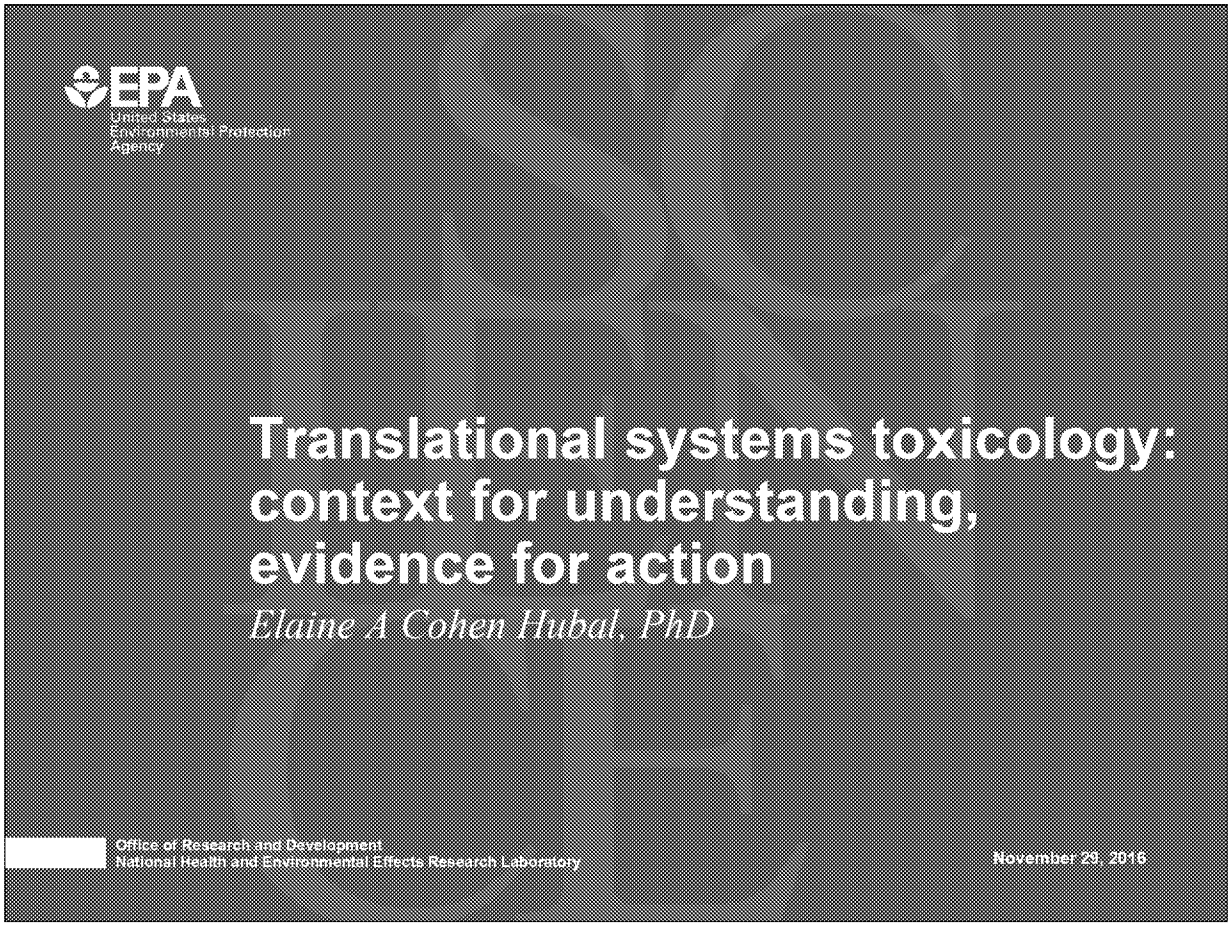
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Translational systems toxicology:
context for understanding,
evidence for action
Elaine A Cohen Hubal, PhD
Office of Research and Development
National Health and Environmental Effects Research Laboratory
November 29, 2016

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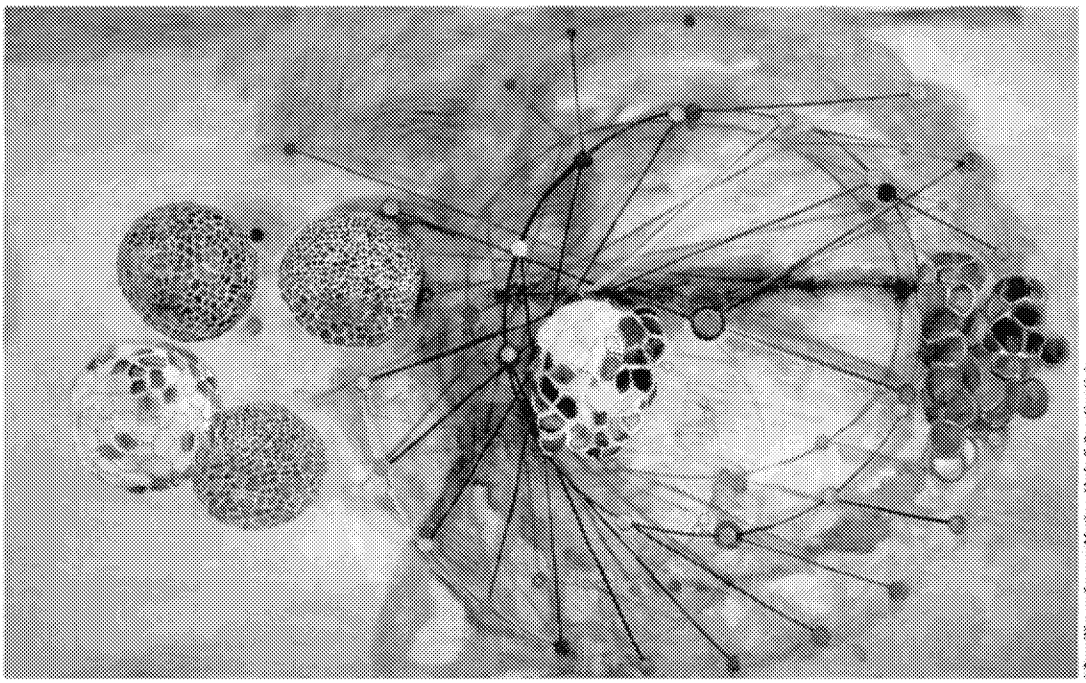
It's complex…



© Terry Winters, Courtesy Matthew Marks Gallery, New York

Eureka, 1988-91, Oil on linen, 96 x 156 inches

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Terry Winters

- Winters has exhibited widely since the early 1980s.
- He “is interested in the organizing structures and systems beneath the seeming randomness of nature’s complexity.”
- A wide range of themes are referenced, from the architecture of biological and living systems to the new spatial orders of data visualization.
- His motifs suggest cellular aggregates, successive stages of embryonic development, or emergent crystal formations.
- His paintings are metaphors for social structures, means of communication, and modes of living.
- “Eureka” was used on the cover of Biological Psychology: a general introduction to the interaction of biological systems and behavior.

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The Matrix

- 'What" defined by NRPs through StRAPs and Roadmap
  - Decision context (regulatory, public health, etc)
  - Priority outcomes (birth defects, neurodevelopmental, metabolic, cancer, endocrine)
  - Priority exposures (chemicals, mixtures/groups, nonchemical)
- "How" defined by LC capacity to translate advances in science and technology

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Programmatic and Organizational Experience

- Leading Change
  - **Experience**: dNPD CSS, Acting Director ISTD
  - **Approach**: Understand mission, Brainstorm, Present straw, Listen, Iterate
  - **Goal**: Compelling vision, Achievable outcomes
- Leading People
  - **Experience**: dNPD CSS, Acting Director ISTD
  - **Approach**: Identify individual strengths, Support professional growth, Build teams, Advocate for productive teams
  - **Goal**: Build critical mass in expertise and enable world class science to achieve mission
- Business Acumen
  - **Experience**: ORD Management Council, CSS Budget Development, NHEERL Budget Execution
  - **Approach**:
    - Learn what is in your sphere of control, what is not
    - Prioritize, make decisions
    - Go directly to primary sources
    - Follow up, follow up, follow up
  - **Goal**: Enable Science and Achieve results in a **complex and dynamic organizational environment**

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Leading Change, Leading People

- **Challenge:** Develop an integrated vision for research to enable EPA to anticipate and address impacts of new and existing chemicals.
- **Action:** Over an 18 months, led extensive engagement process to brainstorm and formulate integrated strategic path for CSS
  - Chaired countless meetings with LC management and senior scientists
  - Conducted meetings to involve Program and Regional partners
  - Worked iteratively to identify and articulate a common path forward to accommodate disparate partner and stakeholder objectives.
  - Solicited, distilled, incorporated input from a broad array of stakeholders.
  - Coordinated with OCSPP and ORD leadership to scope NAS study on evaluating chemical alternatives
  - Collaborated across EPA to develop 3 innovative STAR grant solicitations
  - Developed final language for scientific scope of EPA/NSF lifecycle center solicitation
- **Result:**
  - CSS restructured and focused to be responsive to Agency needs.
  - Compelling vision, purpose, and anticipated impacts clearly articulated
  - ORD LCs began to implement in advance of the FY16-19 StRAP.

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Achieving Results, Business Acumen

- **Challenge:** Ensure viability and support implementation of CSS StRAP. Ensure delivery of outputs, within constraints of a complex matrix organization.
- **Action:** Led effort to put in place the infrastructure to support LC implementation of strategic changes and direction for the CSS program
  - Realigned budget structure - working with OPARM (6 month effort)
  - Initiated development of project plans to ensure \clear commitment to resource and support the research projects across matrix.
  - Harmonized corporate resources with StRAPs: Through role on ORD MC, identified processes that need to be informed by NRP commitments (Cap Equip, OWEP).
- **Results:**
  - Budget realignment process in place for the other NRP realignments
  - Project plan development served as a pilot
  - An inventory of capital equipment was developed, timeframe for the process better aligned with budget allocation timeframe, and criteria for purchasing equipment includes commitments for outputs
  - Hiring decisions being made to build scientific capacity for CSS where there were critical gaps.

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Building Coalitions

- **Challenge:**
  - EPA requires science, information, and tools to incorporate consideration of early lifestage vulnerabilities to support decisions and actions that protect children's wellbeing.
  - ORD leadership is required to bring the science generated outside the Agency together with targeted information generated by EPA to build predictive capacity.
- **Action:**
  - Convened working group (6 ORD NRPs, 5 LCs, OCHP and other program partners).
  - Developed a cross-cutting inventory of the ORD research portfolio;
  - Developed CEH Roadmap research topics and key science questions;
  - Conducted a gap analysis and identifed priority research needs.
- **Result:**
  - Stronger bridges to EPA partners and stakeholders - SAB applauded the Roadmap and noted ORD's unique niche and important leadership role
  - Science required for EPA actions - Administrator noted the importance of this activity and of making sure that EPA gets this right.

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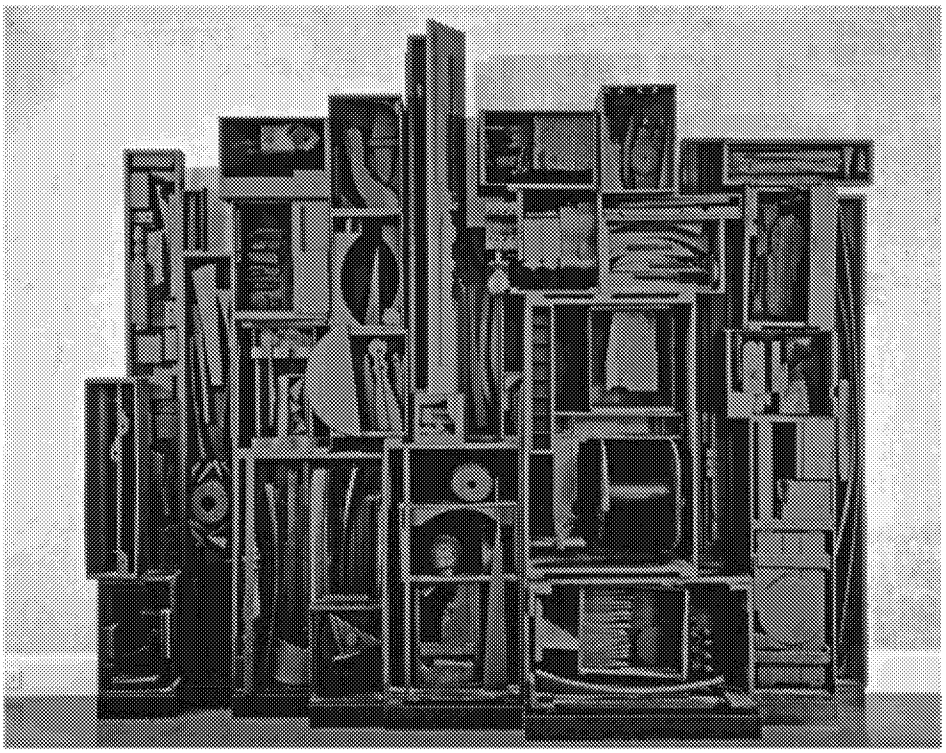
It's diverse and holistic…



Sky Cathedral, 1958. Louise Nevelson, Painted wood 11' 3 1/2" x 10' 1/4" x 18"s

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Louise Nevelson

- Nevelson found her fame creating wooden structures, in the 1960s and 1970s.
- Nevelson purposefully selected wooden objects for their evocative potential to call to mind the forms of the city, nature, and the celestial bodies.
- The various boxes that make up the structure also work to contain the seeming chaos of the assemblage. She purposely painted the entire sculpture black to unify the work.
- While the individual pieces had an intimate scale, they became monumental when viewed holistically within the combined environment of the assemblage.
- She later explored industrial materials like plexiglass, aluminum, and steel. These new materials allowed her to expand the scale and complexity of her works,

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Scientific Expertise and Interest

- In all of the research that I have conducted over the last 25 years, I have applied engineering (i.e., integrated systems) principles and a trans-disciplinary approach to characterize and evaluate biological and environmental systems.

- My primary expertise and research interest is in understanding and predicting complex relationships between environmental factors and health outcomes with an emphasis in vulnerable populations and life stages.

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Integrated Systems Research

Biologically relevant exposure and dose:

- Mass-transport and PBPK models to predict toxicity of inhaled gases
- Dermal exposure measurement methods and dermal uptake models
- Biomarkers of exposure
- Exposure science to inform computational toxicology and 21stC risk assessment

Tools for toxicology and exposure assessment:

- Tools for chemical prioritization – Intake-to-Production Ratio, Exposure ToxPi, biogeographical methods applied for mixtures, ExpoCast
- Data models, ontologies, multi-factorial data visualization

Human Variability:

- Factors influencing exposure of children to chemicals
- Life-stage approach to children's health risk assessment
- Vulnerability factors and cumulative risk assessment for human and ecological receptors (including nonchemical stressors)

Pathways:

- Mechanistic indicators of childhood disease

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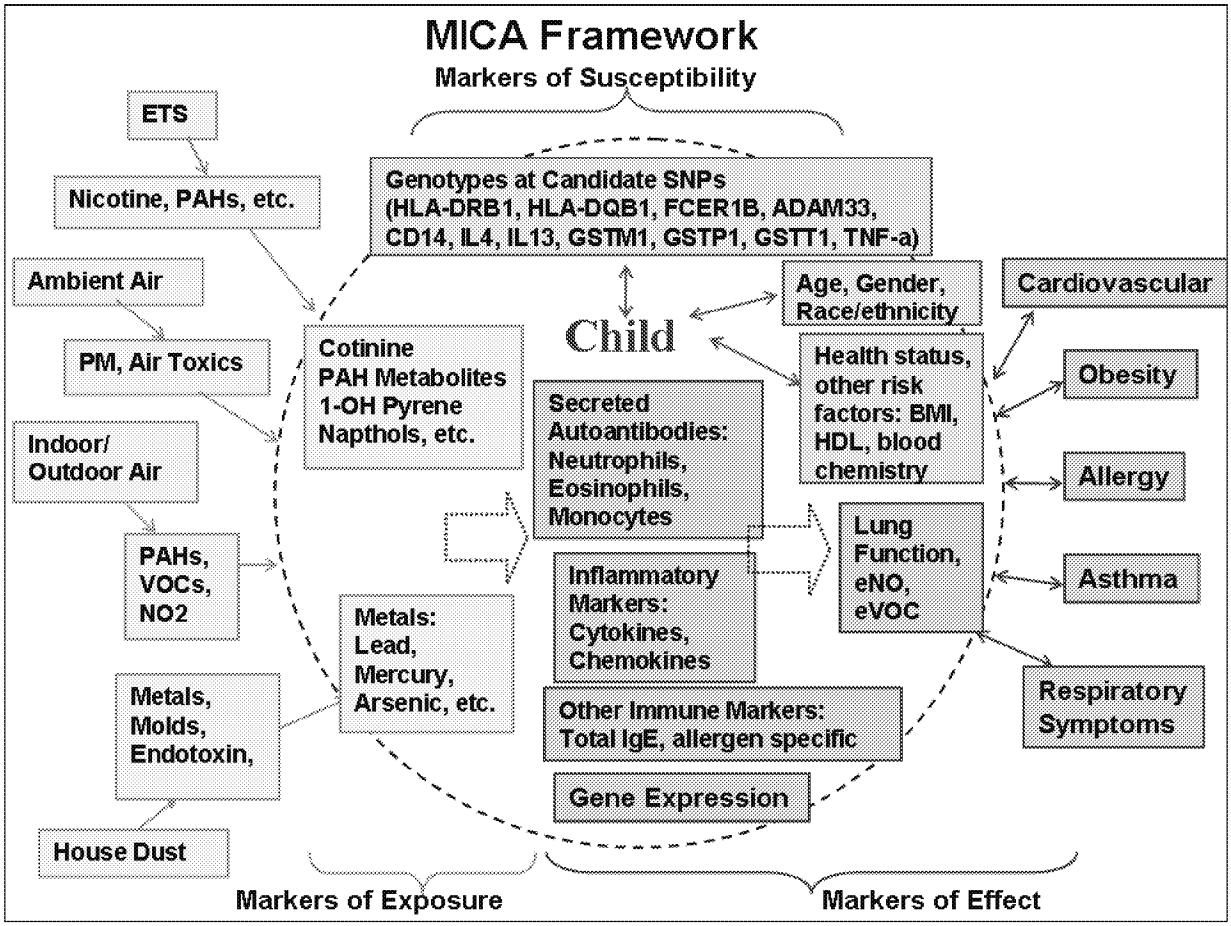
- SVOCs, Pesticides, PBDEs, Phthalates, nanomaterials


MICA Framework
Markers of Susceptibility
ETS
Nicotine, PAHs, etc.
Ambient Air
PM, Air Toxics
Indoor/
Outdoor Air
PAHs,
VOCs,
NO2
Metals,
Molds,
Endotoxin,
House Dust
Genotypes at Candidate SNPs
(HLA-DRB1, HLA-DQB1, FCER1B, ADAM33,
CD14, IL4, IL13, GSTM1, GSTP1, GSTT1, TNF-a)
Cotinine
PAH Metabolites
1-OH Pyrene
Napthols, etc.
Metals:
Lead,
Mercury,
Arsenic, etc.
Child
Age, Gender,
Race/ethnicity
Health status,
other risk
factors: BMI,
HDL, blood
chemistry
Secreted
Autoantibodies:
Neutrophils,
Eosinophils,
Monocytes
Inflammatory
Markers:
Cytokines,
Chemokines
Other Immune Markers:
Total IgE, allergen specific
Gene Expression
Lung
Function,
eNO,
eVOC
Cardiovascular
Obesity
Allergy
Asthma
Respiratory
Symptoms
Markers of Exposure
Markers of Effect

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It's Context…

What does ISTD do?
&
What does ART have to do with it?

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Why context matters…

"Art is not out of context and separate from the world."
George Scheer, cofounder Elsewhere

Neither is toxicology

"…biological modeling emphasizes context specific levels of abstraction and relies on experimental observations to decide if a particular model is useful."
Kirk et al, (2015) Systems biology (un)certainties. Science Vol 350:6259.

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ISTD Vision and Mission: to Enable and Support Agency Actions

- Conduct innovative systems science research to:
  - Understand the role of exposure to environmental contaminants on human health impacts
  - Translate emerging scientific knowledge and technologies to advance tools in toxicology for evaluating and predicting potential for adverse outcomes.
- Integrate advanced experimental and computational approaches to examine complex stressor-biological interactions across multiple levels of biological organization and identify early indicators of adversity.
- Provide mechanistic linkages between exposure, target dose and response essential for designing, interpreting, and translating environmental health studies to inform public health decisions.
- Develop predictive tools (functional assays, biomarkers, accessible data and computational models) to support science-based decisions.

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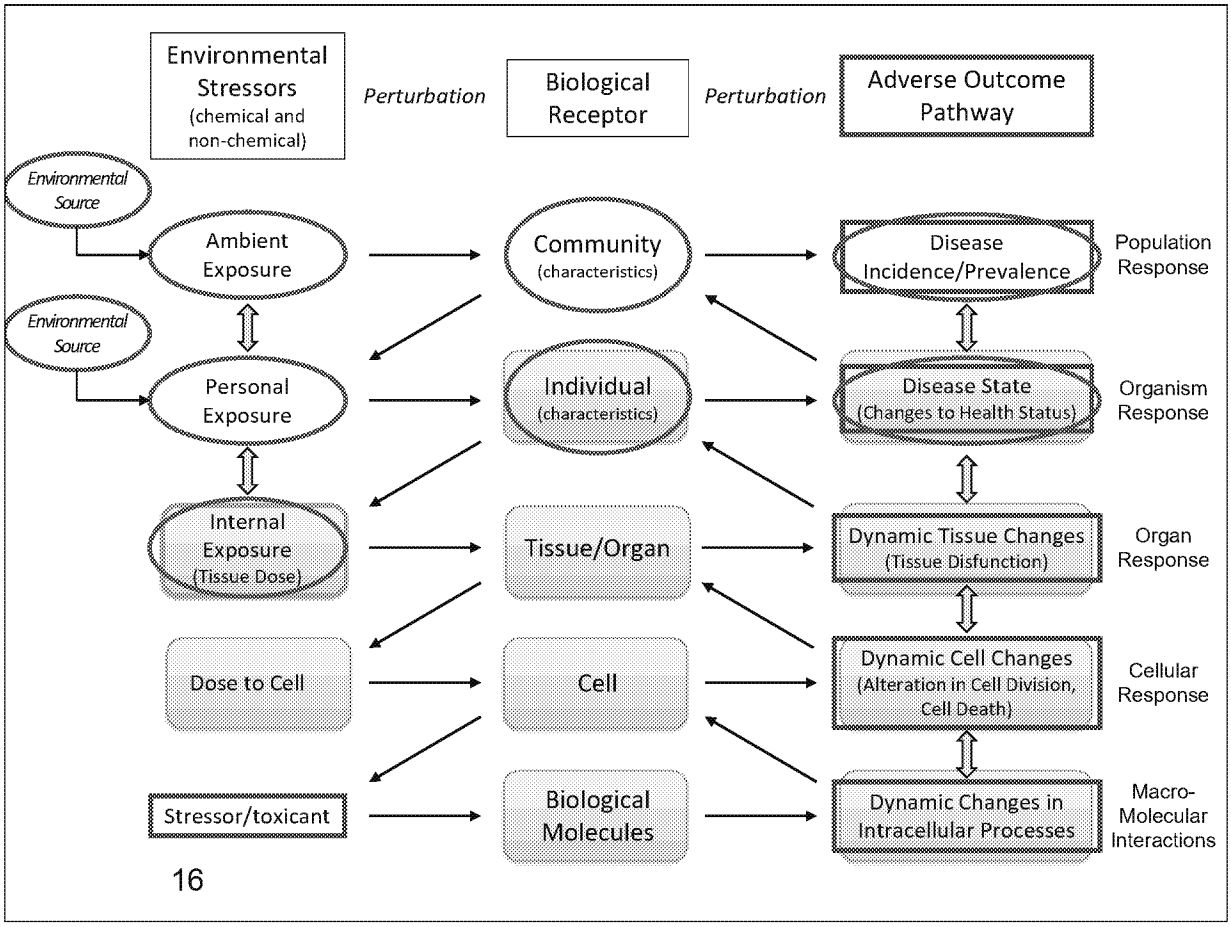

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Concept for integrated CEH research in ORD. Systems theory provides the foundation for linking exposure science, toxicology, and epidemiology to study, characterize, and make predictions about the complex interactions between children and environmental stressors across the course of development. Multifactorial exposures to individuals, communities, and populations are captured horizontally from left to right (blue circles are elements of the source-receptor-outcome paradigm), while outcomes are captured vertically from bottom to top (red boxes are elements of the adverse outcome pathway framework). Kinetics and dynamics of these complex systems processes are not depicted, but are required to meet the objective of moving toward development of predictive tools for supporting risk-based decisions.

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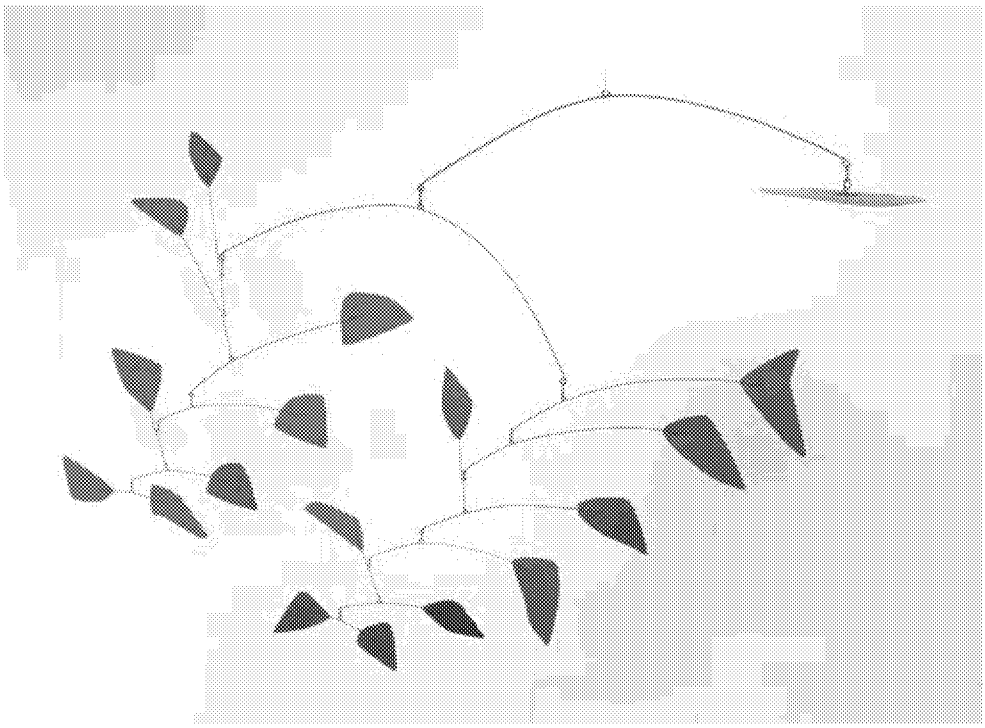
It's kinetic and dynamic…



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Red Sumac, Alexander Calder

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Alexander Calder

- Calder was an American sculptor, trained in mechanical engineering, who redefined sculpture by introducing the element of movement with hanging works called "mobiles."
- Composed of pivoting lengths of wire counterbalanced with thin metal fins, the appearance of the entire piece was randomly arranged and rearranged in space by chance simply by the air moving the individual parts.
- Calder succeeded in integrating natural movement into sculpture by assembling elements that balance themselves naturally by weight, surface area, and length of wire "arm." The basic equilibrium he struck guarantees compositional harmony among the parts, no matter their relative positions at any given moment.

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ISTD Research Areas of Excellence

- **Biological Pathways:** Elucidating and translating mechanistic information linking molecular initiating events, intermediate key events, and phenotypic outcomes.
- **Biologically Relevant Exposure and Dose:** Identifying integrated measures of exposure and dosimetry for translation of toxicity data to assess potential for adverse outcomes.
- **Advanced Tools for Toxicology:** Advancing complex experimental systems, assays, biomarkers, and computational models to translate understanding of biological mechanisms to evaluate and predict potential for adverse impacts.
- **Human Variability:** Considering understanding of variability in dosimetry and response associated with lifestage, genetics, epigenetic modifications, polymorphisms and microbiome function.

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Highlights of current ISTD research

- **Advancing Rapid Methods to Evaluate Neurotoxicity**
  - Zebrafish the New Laboratory Rat
  - Novel *In Vitro* Assays
- **Understanding Impacts of Chemical Exposures on Development**
  - Virtual Embryo (
  - Life PBPK Stage Model
- **Evaluating Interactions of Real World Chemical Mixtures**
  - Mixtures in Drinking Water
  - Complex Mixtures in Air
- **Considering Bioavailability to Link Exposure with Health Effects**
- **Identifying Biomarkers of Susceptibility and Early Effects of Adversity**
  - Cancer
  - Metabolic Disease
- **Making Information Accessible for the Research Community**
  - AOPwiki

It's mission driven…

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DALE CHIHULY, PERSIAN SEAFORM CEILING

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Dale Chihuly

- Chihuly's sought a technical solution to the problem of fragility …to strengthen glass by forming it in a grooved mold, reinforcing the fabric much as corrugation adds firmness to cardboard.

- Watching the process of glass blowing and the effect of gravity on the hot and supple materials is like witnessing a time-lapse recording of proliferating sea life, the glass forms germinating like palpable living organisms. The resultant shape of the *Seaforms* is a whorl of arabesques springing outward from a source, ... there is no sense of "ponderation," of weight distributed centrally and securely. Because their shapes are so amorphous and irregular,…, they refute classical balance, achieving a kind of delicate equipoise." –Joan Seeman Robinson

- "I love to go to the ocean and walk along the beach. If you work with hot glass and its natural properties it begins to look like something that came from the sea." –Chihuly

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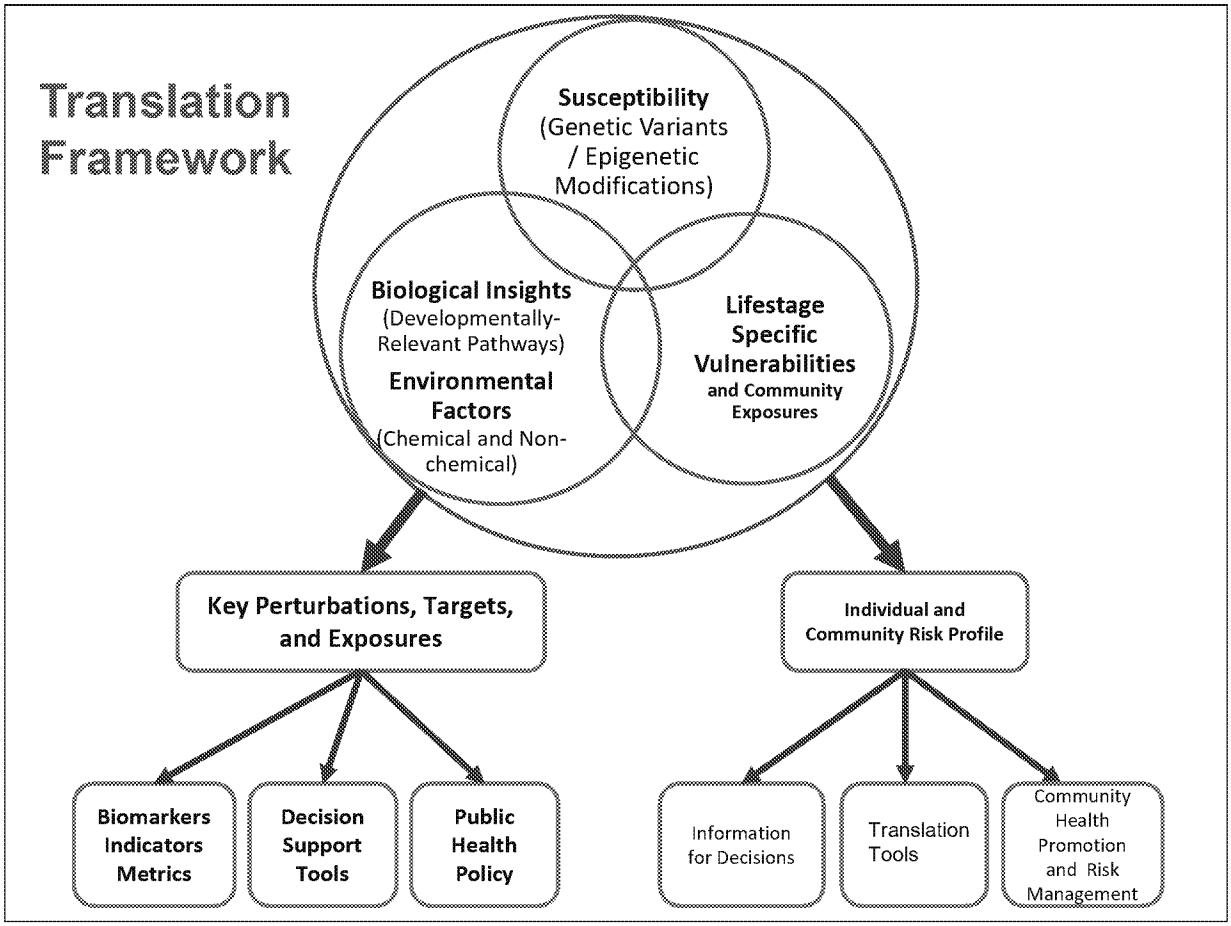

The Agency and stakeholders require translation of cutting edge science to incorporate consideration of early lifestage susceptibility and vulnerability into decision making. The translation framework presented in Figure x (adapted from McCarthy et al., 2008) consider two routes by which ORD research will provide required information and tools. In the first, identification of toxicity pathways coupled to identification of important environmental factors (exposures) provides new opportunities to inform decision making and public health protection at the population level. Decision support tools developed along this route may include: (1) biomarkers, metrics, and indicators for measuring and monitoring environmental exposures as well as providing early indication of toxicological impacts; (2) extrapolation models for risk assessment based on detailed understanding of relevant environmental stressors and associated perturbations to toxicity pathways; and (3) public policy to prevent or mitigate exposures to protect human health and welfare. The second translational route lies through using knowledge of individual patterns of exposure and disease predisposition to develop community-based approaches to health promotion and risk management. Here, environmental health research and public policy can only fully empower communities to manage risks by providing a clear understanding of important exposures and where these can be locally controlled. Considerations of individual variation based on genetic susceptibility, life stage, and interaction of nonchemical stressors is required context for both routes and for holistic assessment of risk factors associated with complex environmental disease. By requiring characterization of biologically relevant exposure, this framework facilitates translation of advances and findings in computational toxicology to information that can be directly used to support risk assessment for decision making and improved public health. In addition, application of this framework will inform design of future exposure and epidemiology studies such that data gaps along all levels of biological organization (i.e., both at population and molecular levels) are targeted in a systems-based fashion. Such a strategic implementation of exposure and epidemiology studies is required to ensure efficient use of resources committed to health studies. Further, over time and with the generation of requisite exposure data, this framework will facilitate elucidation of gene–environment interactions and important environmental contributions to complex disease.

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Context for understanding – Higher throughput and alternative toxicity tests

- Mechanistic context for interpretation of HTT
  - homeostatic, normal biology,
  - dynamics, cellular environment
  - tissue specific pathways/response
- Context for real world relevance
  - Kinetics – AOP Pulse
  - Dose to model systems
  - Function (relationship of tipping points to phenotypes)
- Context to bridge between toxicology and epidemiology
  - Transcriptomic signatures/ biomarkers of key events, early effects
  - Stable markers of exposure (epigenetic modifications, other exposomic markers)
- Context for considering susceptibility/variability
  - Lifestage, Critical windows, Sex
  - Genetics (genotypes that modify exposures, that modify effects)
  - Non chemical stress, Psychosocial, Disease state,

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Evidence for action – partner to BRIDGE toxicology and epidemiology for EPA PUBLIC HEALTH decisions

- EPA's investments in human studies have identified important associations.
- EPA 'big data' approaches – including research in HTT screening, AOPs and virtual tissue modeling is advancing efficient methods for translating findings in biology to predict effects of environmental exposures
- **Integrated approach (*in vitro*, animal models, human studies)** required to examine potential interaction and impact of multiple stressors on, for example, ASD pathology and etiology, including understanding of impacts of chemical exposures on related intermediate endpoints.
- Some opportunities:
  - Postulate AOPs and AOP networks based on genetic risk factors of ASD and other neurological outcomes
  - Develop assays to cover biological endpoints relevant to neurological outcomes, screen chemicals for these endpoints
  - Develop HTP methods that model GxE interactions for data driven hypothesis development
  - Apply experimental models of ASD to explore gene-environment interactions (i.e., animal, stem cell systems) and to identify biomarkers

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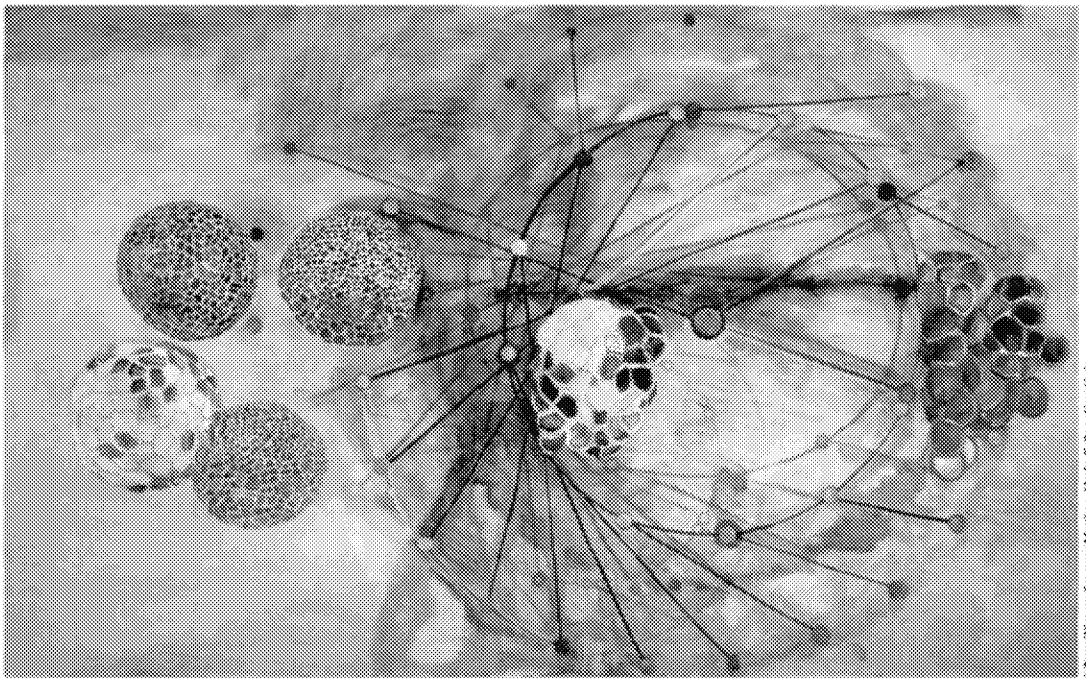

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Eureka, 1988-91, Oil on linen, 96 x 156 inches

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